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UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: Patricia Ann Duffy *Art Unit:* 1645

In re:

Applicant: James Brady

Serial No.: 09/832,159

Filed: April 10, 2001

DECLARATION OF UNOBVIOUSNESS

I hereby certify that this correspondence is being deposited with the United States Postal Service by First Class Mail on the date indicated above and is addressed to the Assistant Commissioner of Patents and Trademarks, Washington, D.C. 20231

10/14/03

ILYA ZBOROVSKY

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

I, ***Vadim DAVANKOV***, residing at Leningradskoe Shosse, 112/1, K3 KV825, Moscow 125445, Russia, am a coinventor of the above identified application. I hereby confirm that I am Head of Laboratory of Stereo Chemistry of Sorption Processes of INEOS of Russian Academy of Sciences, Moscow, a member of Russian Academy of Natural Sciences, Professor and Doctor of Science. I am also a member of American Chemical Society, titular member of IUPAC, Vice Chairman of Scientific Counsel on Adsorption Chromotography at the Russian Academy of

Sciences, and Chairman of the Section of the Liquid of Chromotography. I am a member of the Editorial Board of magazines, inventor of and coinventor of patents including U.S. patents, and author and coauthor of numerous scientific applications.

I familiarized myself with the Office Action in the above identified application, in which the Examiner applied some grounds for objections and rejections. In connection with this, I would like to express my opinion about unobviousness of the present invention as well as about other issues.

As for the Examiner's formal rejection of the claims, I believe that it is not necessary to provide the information about the actual number of particles amount of the material in the system, since it depends on practical requirements and clinical parameters for passing blood through the polymeric material, in particular the quantity of blood, the speed of passage of blood, etc., etc. I believe that the type of beads or materials used for producing the beads are disclosed in the application on page 12, and defined in claims 9, 10 and 11. The relative functions and/or structure of hydrophobic/hydrophilic, mesoporous/macroporous materials, as well as binding of endotoxins or superantigens and cytokynes are generally known

in sorption technique. A hydrophobic/hydrophilic material is, correspondingly, a material which repels aqueous media or attracts aqueous media. It is also well established that polar polymers are hydrophilic and non-polar polymers are hydrophobic. The mesoporous and microporous particles are also known in the art, and also on page 10, in paragraph 2 and page 11 in paragraph 2 the corresponding description is provided, which would be sufficient for practicing of the invention. The nature of binding of endotoxin as well as superantigens and cytokines is described in the specification, and an example is given to illustrate this feature. Also, the corresponding part of the specification has been amended to clarify this feature. The background of the invention also specifically explains the relationship between endotoxins, superantigens, cytokines, and infection or sepsis.

I therefore declare, based on my experience and expertise, that in my opinion the application sufficiently answers the questions raised by the Examiner and sufficiently discloses the invention to be practiced by a person of ordinary skill in the art.

As for the patents applied by the Examiner against the claims, the patent to Matson has a reference to inflammatory mediators, such as

cytokines, and endotoxins, and discloses a possibility of using various particles. However, it does not disclose a system in which a particulate hemocompatible material includes a first group of macroporous particles which are hydrophobic and positively charged to provide adherence of endotoxins to an inner surface of the particles, and a second group of mesoporous particles which are hydrophobic and not charged so that cytokines and superantigens adhere to an inner surface of the particles of this group, so as to simultaneously purify blood from endotoxins, cytokines and superantigens and thereby to treat serious infections and sepsis. The general statement about the possibility of using certain particles does not provide any hint in the patent to Matson for a particular hemocompatible material which would be similar or identical to the material disclosed in this present application.

The patent to Davankov teaches sorbents for removing blood toxicants, comprising a hypercrosslinked styrene resin with a surface modified to be biocompatible. However, this reference also does not teach the above mentioned new features of the present invention.

Based on my expertise and experience, I hereby believe that it can not be considered as obvious to arrive at the invention disclosed in the present application either from the teaching of the patent to Matson, or from

the teaching of the patent to Davankov, or from any combination of these references, since both references are completely silent of the new features of the present invention defined in the claims. It is believed that the references can neither anticipate the present invention nor make it obvious.

I am also enclosing my curriculum vitae to confirm my qualification to sub it the above-presented about the issues raised by the Examiner in the Office Action.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that those statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Oct. 13, 2003

V. DAVANKOV

CURRICULUM VITAE

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Personal data: Born - November, 20, 1937 in Moscow, USSR
Married, two children: aged 42 and 29

Academic Degrees:

The Technical University in Dresden, DDR; 1962, Dresden;
Ph.D - 1966, "Synthesis and Investigation of Dissymmetric Ion Exchange Resins", INEOS, Moscow;
Dr.Sc. - 1975, "Ligand Exchange Chromatography of Racemic Mixtures", INEOS, Moscow.
Professor - 1980 - INEOS, Moscow.
Visiting Professor - 1993 - University Paris Nord, Paris, France;
1997 - Nankai University, Tiantzin, China

Professional Experience:

1975-present: Head of Department for Stereochemistry of Sorption Processes at the Nesmeyanov Institute of Organo-Element Compounds, Moscow;

1962-1954 successively: Post-graduate student, junior research fellow, senior research fellow, head of Department, deputy Director (1988-1994) of the Nesmeyanov Institute of Organo-Element Compounds, Russian Academy of Sciences.

Membership in Scientific Associations and Working groups:

since 1992 - Elected member of the American Chemical Society.

since 1992 - Associated member (since 1996 -titular member) of IUPAC, (Analytical Chemistry);

since 1989 - Chairman of the Scientific Council on Chromatography at the Russian Academy of Sciences;

since 1983 - Chairman of the Section for Molecular Liquid Chromatography of the above Council;

Member of editorial boards of the following journals:
"Zhurnal Phisicheskoi Khimii" (Russia), "Chirality", "Journal of Chromatography", "Chromatographia", "Reactive and Functional Polymers", "Journal of Biochemical and Biophysical Methods"; for several years in the past also of journals "BioTechniques", "Journal of Pharmaceutical and Biomedical Analysis", "Journal of High Resolution Chromatography", "Isolation and Purification".

Awards: 1978 - M.Tswett Medal for Chromatography, USSR Acad. Sci.

1992 - Diploma for the scientific discovery "Participation of achiral molecular structures in the chiral recognition of enantiomers by a chiral selector", Russia

1996 - State Award of Russian Federation for Science and Technology.

1999 - "Chirality Medal 1999" - international gold medal for outstanding contributions to the field of stereochemistry

Fields of Scientific Interest:

chromatographic resolution of enantiomers,
ligand exchange chromatography,
synthesis of polymer-coated macroporous silica gels as new type of HPLC packing materials,
synthesis and investigation of hypercrosslinked polystyrene networks and adsorbents,
stereochemistry of coordination compounds,
enantioselective catalysis,
polymers for hemoperfusion.

Most important achievements:

1. As early as 1968, Davankov filed patents on resolution of racemic amino acids into constituent enantiomers. With the HPLC technique not jet developed at that time, he prepared his CSPs by binding chiral amino acids to crosslinked polystyrene beads and, as a consequence, his experiments were of micro-preparative scale. He suggested complexing to transition metal ions, e.g., copper(II) ions, as a means of enhancing interactions between the bonded chiral selector and the enantiomers to be separated, which comprised the distinguishing feature of ligand exchange chromatography. Due to extremely high enantioselectivity of formation of the above mixed-ligand complexes, he was able to demonstrate a base-line resolution of 0.5 g D,L-proline into enantiomers, as well as enantiomers of numerous amino acids, hydroxy acids, amino alcohols, diamines. H. Walton called these results "triumph of ligand exchange chromatography". A series of intensive studies into the mechanism of chiral recognition of amino acids followed, which resulted in the discovery of enantioselectivity in the formation of ternary copper(II) complexes incorporating amino acids, diamines and dicarbonyl compounds. For the first time, kinetic enantioselectivity of formation of labile complexes was demonstrated. While synthesizing various CSPs, Davankov suggested dynamic coating of conumercially available reversed phase HPLC columns with hydrophobic chiral ligands. These "Davankov columns" remain popular and useful in the enantiomeric analysis of natural and non-natural amino acids (Regis Technologies, USA). Very important are studies into mechanism of chiral recognition and, especially, discovering the "Participation of achiral molecular structures in the chiral recognition of enantiomers by a chiral selector" (Diploma for Scientific Discovery, USSR. 1992).

Results of above studies in the field of stereochemistry and chiral ligand exchange chromatography are summarized in a series of systematic reviews, for instance:

Ligand Exchange Chromatography, V.A.Davankov, J.D Navratil, H.F.Walton, CRC-Press, Boca Raton, USA, 1988

30 Years of chiral ligand exchange, V.A Davankov, **Enantiomer, 5** (2000) 209-223

2. Equally important and unexpected are introduced by Davankov "hypercrosslinked" polystyrene networks, peculiar hydrophobic materials which show strong swelling in any liquid media, including water. New generation of polystyrene-type adsorbing materials emerged (manufactured by Purolite Int., Wales, UK) on the base of these novel rigid spacious networks. They proved extremely useful in large scale adsorption technologies, as a novel solid phase extraction materials in analytical chemistry, and as perspective column packing in HPLC. The concept also allowed the synthesis of "nanosponges", fundamentally new, intramolecularly hypercrosslinked, macromolecular species.

Hypercross-linked polystyrene and its potentials for liquid chromatography: a mini-review, V.Davankov, M.Tsyurupa, M.Ilyin, L.Pavlova, **J. Chromatogr. A, 965** (2002) 55-73

Sorption of organic compounds from aqueous media by hypercrosslinked polystyrene sorbents "Styrosorb", M.P.Tsyurupa, L.A.Maslova, A.I Andreeva, T.A.Mrachkovskaya, V.A.Davankov, **Reactive Polymers, 25** (1995) 69-78

Hypercrosslinked polystyrene: A polymer in a non-classical physical state, A.V.Pastukhov, M.P.Tsyurupa, V.A.Davankov, **J. Polymer. Sci. B, Polymer Phys., 37** (1999) 2324-2333

Formation of regular clusters through self-association of intramolecularly hypercrosslinked polystyrene-type nanosponges, V.A.Davankov, G.I.Timofeeva, M.M Ilyin, M.P.Tsyurupa, **J. Polymer Sci., Part A: Polymer Chem., 35** (1997) 3847-3852

3. Davankov developed a highly effective polymeric adsorption material for a selective removal of toxic proteins ("middle molecules") from blood. Having special hemocompatible coating of the surface, the material successfully passed clinical trials in the USA. It offers new perspectives in treatment of patients with kidney failure, septic shocks, etc. A company RenalTech Int., (New York) aims commercialization of this new technology (see web-site www.renaltech.com).
V.Davankov, L.Pavlova, M.Tsyurupa, J.Brady, M.Balsamo, E.Yousha. Polymeric adsorbent for removing toxic proteins from blood of patients with kidney failure, **J. Chromatogr. B, 739** (2000) 73-80

4. In the year 1996 Davankov started a scientific discussion on reconsideration of the physical meaning of corrected retention volume, the most important retention parameter in gas chromatography. As a result, incorrect interpretation and improper use of these values, that lasted for over 50 years, was revealed and corrected, which opens clear way for using gas chromatography as a precise measurement technique for determination of thermodynamic parameters, in addition to the traditionally successful use of GC as an outstanding analytical technique.
V.A.Davankov, Retention parameters in gas chromatography, IUPAC Recommendations 2001, Part B. **Pure & Appl. Chem., 73** (2001) 982-992

5. In recent years, a series of new chiral P,N-bidentate ligands of phosphite and amino phosphite type have been synthesized and successfully tested in numerous asymmetric catalysis processes, showing high chemical and enantiomeric yield (up to 98 % ee).
Novel *P,N*-bidentate phosphite ligands in asymmetric catalysis, K.N. Gavrilov, O.G. Bondarev, A.V. Korostylev, A.I. Polosukhin, V.N. Tsarev, N.E. Kadilnikov, S.E. Lyubimov, A.A. Shiryaev, S.V. Sheglov, H.-J. Gais, V.A. Davankov, **Chirality, in press**

Publications - V.A. Davankov authored and co-authored more than 500 scientific papers and patents. He also published a book on "Ligand Exchange Chromatography" (CRC-Press, USA, 1988) and contributed many chapters to seven collective monographs

Some most important recent publications of V.A.Davankov in international journals:

401 Sorption of organic compounds from aqueous media by hypercrosslinked polystyrene sorbents "Styrosorb", **Reactive Polymers**, 25/1, 69-78, 1995. M.P.Tsyurupa, L.A.Maslova, A.I.Andreeva, T.A.Mrachkovskaya, V.A.Davankov

402 Use of hypercrosslinked polystyrene sorbents "Styrosorb" for solid phase extraction of phenols from water, **Fresenius' J. Anal. Chem.**, 352, 7/8, 672-675, 1995, M.P.Tsyurupa, M.M.Ilyin, A.I.Andreeva, V.A.Davankov

404 NMR investigations of the enantiomeric excess effects in solutions with weak intermolecular association, **Chirality**, 7/5, 326-330, 1995, E.I.Fedin, V.A.Davankov

418 From a dissolved polystyrene coil to an intramolecularly hypercrosslinked "nanosponge", **Macromolecules**, 29/26, 8398-8403, 1996, V.A.Davankov, M.M.Ilyin, M.P.Tsyurupa, G.I.Timofeeva, L.V.Dubrovina

423 Polymeric materials with a novel type of porosity, in **Characterization of Porous Solids IV**, Eds. B.McEnaney, T.J.Mays, J.Rouquerol, F.Rodriguez-Reinoso, K.S.W.Sing, K.K.Unger. The Royal

Society of Chemistry, 1997, 398-405, M.P.Tsyurupa, A.S.Shabaeva, L.A.Pavlova, T.A.Mrachkovskaya, V.A.Davankov

425 The true physical meaning of the corrected retention volumes in GC. **Chromatographia**, 44, 5/6, 279-282, 1997, V.A.Davankov

427 Hypercrosslinked polystyrene: a polymer in a non-classical physical state. **Doklady Russian Acad. Sci.**, 352/1, 72-73, 1997, M.P.Tsyurupa, A.V.Pastukhov, V.A.Davankov

429 The nature of chiral recognition: Is it a 3-point interaction?, **Chirality**, 9/2, 99-102, 1997, V.A.Davankov

431 Analytical chiral separation methods, **Pure & Appl. Chem.**, 69/7, 1469-1474, 1997, V.A.Davankov

433 Formation of regular clusters through self-association of intramolecularly hypercrosslinked polystyrene-type nanosponges, **J. Polymer Sci., Part A: Polymer Chem.**, 35, 3847-3852, 1997, V.A.Davankov, G.I.Timofeeva, M.M.Ilyin, M.P.Tsyurupa

456 Averaging the pressure and flow rate of the carrier gas in a gas chromatographic column, V.A.Davankov, L.A.Onuchak, S.Yu.Kudryashov, Yu I.Arutyunov, **Chromatographia**, 49, No 7/8, 449-453, 1999

458 Investigation of the properties of hypercrosslinked polystyrene as a stationary phase for high-performance liquid chromatography, N.A.Pertner, P.N.Nesterenko, M.M.Ilyin, M.P.Tsyurupa and V.A.Davankov, **Chromatographia**, 50, 9/10,611-620, 1999

463 Hypercrosslinked polystyrene: A polymer in a non-classical physical state, **J. Polymer. Sci. B, Polymer Phys.**, 37/17, 2324-2333, 1999, A.V.Pastukhov, M.P.Tsyurupa, V.A.Davankov

474 Polymeric adsorbent for removing toxic proteins from blood of patients with kidney failure, V.Davankov, L.Pavlova, M.Tsyurupa, J.Brady, M.Balsamo, E.Yousha, **J. Chromatogr. B, Biochemical Applications**, 739 (2000) 73-80

490 Method of and material for purification of physiological liquids of organism, and method of producing the material, **Pat. USA 6,136,424**, Oct.24 2000, V.Davankov, M.Tsyurupa, L.Pavlova, D.Tur

494 30 Years of chiral ligand exchange, V.A.Davankov, **Enantiomer**, 5/3-4, 209-223 (2000)

495 Ligand exchange chromatography, V.A.Davankov, **Encyclopedia of Separation Sciences**, III. Chiral Separations, 2369-2380 (2000)

501 Evaluation of a hypercrosslinked polystyrene, MN-200, as a sorbent for the preconcentration of volatile organic compounds in air, M.P.Beya, P.A.Panayotis, V.A.Davankov, **J. AOAC Int.**, 83/3, 579-583 (2000)

504 Complexation properties of aminophosphites bearing phosphorus and nitrogen atoms in six-membered cycles, A.V.Korostylev, O.G.Bondarev, A.Yu.Kovalevsky, P.V.Petrovskii, V.A.Davankov, K.N.Gavrilov, **Inorg. Chim. Acta**, 312, 117-124 (2001)

505 Iminophosphites as new chiral P,N,-bidentate ligands, K.N.Gavrilov, A.I.Polosukhin, O.G.Bondarev, A.V.Korostylev, S.E.Lyubimov, A.A.Shiryaev, Z.A.Starikova, V.A.Davankov, **Mendeleev Commun.**, 2001, 33-35

507 Retention parameters in chromatography, Part B. Retention parameters in gas chromatography, V.A.Davankov, **Pure & Appl. Chem.**, 73, 969-992, 2001

508 Platinum-containing hyper-cross-linked polystyrene as a modifier-free selective catalyst for L-sorbose oxidation, S.N.Sidorov, I.V.Volkov, V.A.Davankov, M.P.Tsyurupa, P.M.Valetsky, L.M.Bronstein, R.Karlinsey, J.W.Zwanziger, V.G.Matveeva, E.M.Sulman, N.L.Vakina, E.A.Wilder, R.J.Spontak, **J. Am. Chem. Soc.**, 123, 10502-10510 (2001)

510 Hypercross-linked polystyrene and its potentials for liquid chromatography, V.Davankov, M.Ilyin, M.Tsyurupa, R.Nosov, *Application of Theory to the Understanding and Practice of Chromatography. An International Symposium in Honor of Dr L.R Snyder*, Ellecom, The Netherlands, June 2001

513 Phosphite derivatives of (2R)-2-pyrolidin-1-yl-butan-1-ol: synthesis, chelation, with rhodium(I) and testing in the palladium-catalysed allylic alkylation, A.I.Polosukhin, O.G.Bondarev, A.V.Korostylev, R.Hilgraf, V.A.Davankov, K.N.Gavrilov, **Inorg. Chim. Acta**, 323/1-2, 55-61 (2001)

515 New chiral phosphite ligands bearing sp^2-nitrogen: complexation properties and Pd-catalysed enantioselective allylic alkylation, A.I.Polosukhin, O.G.Bondarev, S.E.Lyubimov, A.V.Korostylev, K.A.Lyssenko, V.A.Davankov, K.N.Gavrilov, **Tetrahedron: Asymmetry**, 12/15, 2197-2204 (2001)